IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: LEUNG *et al.* Serial No.: 09/988,013 Filed: November 16, 2001 Title: IMMUNOCONJUGATES AND HUMANIZED ANTIBODIES SPECIFIC FOR B-CELL LYMPHOMA AND LEUKEMIA CELLS Group Art Unit: 1643 Examiner: David Blanchard Attorney Docket No.: IMMU:014US2 Confirmation No.: 7681

VIA EFS-WEB

BRIEF ON APPEAL UNDER 37 CFR §41.37

COMMISSIONER FOR PATENTS
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Sir:

This appeal brief is being filed in accordance with the provisions of 37 C.F.R. § 41.37. The Commissioner is authorized to charge the fee of $255.00 under Rule 17(c) for filing of this brief to Deposit Account 18-2056. If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to deposit account 18-2056. Appellants request a one-month extension of time for submission of the brief, and the fee is addressed in the transmittal. If any further extensions of time are needed for timely acceptance of papers submitted herewith, Appellants hereby petition for such extension under 37 C.F.R. §1.136(a) and authorizes payment of any such extension fees to Deposit Account No. 18-2056.

I. REAL PARTY IN INTEREST

The real party in interest in this application is Immunomedics, Inc., as evidenced by an assignment filed in the United States Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellants, the appellants' legal representative, or assignee, which are related to, will directly affect or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Pending claims: 28, 29, 31, 32

Rejected claims: 28, 29, 31, 32

Appealed claims: 28, 29, 31, 32

Canceled claims: 1-27, 30, 33-43

IV. STATUS OF AMENDMENTS

An amendment was filed on December 31, 2007, after a final rejection. An Advisory Action dated January 28, 2008, indicated that this amendment would be entered for purposes of appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 28 is the sole independent claim involved in the appeal. It recites a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody comprising:

(a) comparing the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of two or more human antibodies;

(b) selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody; and

(c) incorporating the framework regions selected in step (b) with the corresponding light and heavy chain complementarity determining regions of the monoclonal antibody to be humanized, to design humanized light and heavy chain variable domain amino acid sequences

wherein the heavy chain FR4 is selected from the human NEWM antibody, the light chain framework regions are selected from the human REI antibody, and the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody.

The specification describes a method of *designing amino acid sequences* in paragraphs 0043 and 0044 (page 10, line 7 to page 11, line 15, emphasis added):

> An important aspect of this invention is that antibody variable domains can be modeled by computer modeling (see, for example, Dion, in Goldenberg *et al.* eds., CANCER THERAPY WITH RADIOLABELED ANTIBODIES, CRC Press, Boca Raton, Fla., 1994), which is incorporated by reference. In general, the 3-D structure for both the mLL22 and hLL2 mAbs are best modeled by homology. The high frequency of residue identities (75.0 to 92.3%) between the deduced primary sequences of mLL2 light chain FR regions and human REI (VK) facilitates this approach because of the availability of crystallographic data from the Protein Data Bank (PDR Code 1REI, Bernstein *et al.*, *J. Mol. Biol.* 112: 535 (1977)), which is incorporated by reference. Similarly, antibody EU (VH) sequences can be selected as the computer counterparts for FR1 to FR3 of the mLL2 heavy chain; FR4 was based on NEWM. As X-ray coordinate data is currently lacking for the EU sequence, NEWM structural data (PDR Code 3FAB) for FRs 1 to 4 can be used, and amino acid side groups can be replaced to correspond to mLL2 or EU (hLL2) as needed. The CDR of the light chain can be modeled from the corresponding sequence of 1MCP (L1 and L2) and 1REI (L3). For heavy chain CDRs, H1 and H2 can be based on 2HFL and 1MCP, respectively, while H3 can be modeled *de novo*. Wherever possible, side group replacements should be performed so as to maintain the torsion angle between Cα and Cβ. Energy minimization may be accomplished by the AMBER forcefield (Weiner *el al.*, *J. Amer. Chem. Soc.* 106: 765 (1984) using the convergent method. Potentially critical FR-CDR interactions can be determined by initially modeling the light and heavy variable chains of mLL2. All FR residues within a 4.5 Å radius of all atoms within each CDR can thereby be identified and retained in the final design model of hLL2.
>
> Once the ***sequences*** for the hLL2 VK and VH domains ***are designed***, CDR engrafting can be accomplished by gene synthesis using long synthetic DNA oligonucleotides as templates and short oligonucleotides as primers in a PCR reaction. In most cases, the

> DNA encoding the VK or VH domain will be approximately 350 bp long. By taking advantage of codon degeneracy, a unique restriction site may easily be introduced, without changing the encoded amino acids, at regions close to the middle of the V gene DNA sequence. For example, at DNA nucleotide positions 157-162 (amino acid positions 53 and 54) for the hLL2 VH domain, a unique AvrII site can be introduced while maintaining the originally ***designed amino acid sequence*** (FIG. 4B).

Paragraph 0067 (page 21, lines 21 to 25) describes comparing the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of two or more human antibodies (emphasis added);

> By ***comparing*** the ***murine variable (V) region framework (FR) sequences*** of LL2 ***to that of human antibodies*** in the Kabat data base (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference,

Paragraph 0067 (page 21, line 25, to page 22, line 8) goes on to describe selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR4 is selected from the human NEWM antibody, the light chain framework regions are selected from the human REI antibody, and the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody:

> the human REI (FIG. 1A, Sequence ID No. 1) and EU (FIG. 1B, Sequence ID No. 2) sequences were found to exhibit the ***highest degree of sequence homology*** to the FRs of VK and VH domains of LL2, respectively. Therefore, the ***REI and EU FRs were selected as the human frameworks*** onto which the CDRs for LL2 VK and VH were grafted, respectively. The ***FR4 sequence of NEWM***, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 ***heavy chain***. Based on the results of computer modeling studies (FIGS. 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (FIG. 1).

Paragraph 0044 (page 11, lines 5-8) describes incorporating the selected framework regions with the corresponding light and heavy chain complementarity determining regions of the monoclonal antibody to be humanized:

> Once the sequences for the hLL2 VK and VH domains are designed, ***CDR engrafting*** can be accomplished by gene synthesis using long synthetic DNA oligonucleotides as templates and short oligonucleotides as primers in a PCR reaction.

Examples 1 to 3 (page 21, line 18, to page 28, line 7) exemplify this process in detail for the humanization of the LL2 antibody.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Rejection of claims 28, 29, 31 and 32 under 35 USC 112, first paragraph, as failing to comply with the written description requirement.

B. Rejection of claims 28, 29, 31 and 32 under 35 USC 102(b) based on Leung *et al.* (US 5,789,554).

C. Rejection of claims 28, 29, 31 and 32 under 35 USC 102(b) based on Leung *et al.* (*Molecular Immunology*, 32(17018):1413-1427 (1995).

Objections for defective oath or declaration and priority, which are not stated as rejections, are raised in connection with rejections 1, 2 and 3.

VII. ARGUMENT

A. <u>The rejection of claims 28, 29, 31 and 32 under 35 USC 112, first paragraph, as failing to provide a written description.</u>

The present application is described in, and properly claims priority to, the 08/289,576 parent, and therefore the declaration is not defective.

At the outset, it is noted that the examiner indicates that the disclosure of the prior-filed application 08/289,576 does not provide adequate support in the manner provided by 35 USC 112, first paragraph, and that therefore the oath or declaration is defective, based on his belief that the present application is a continuation-in-part application. Based on the following discussion with respect to the rejection under Section 112 for lack of written description, it is clear that the present

application is a continuation which is entitled to the priority date of application serial no. 08/289,576. Therefore, a new oath or declaration is not required.

The examiner cites case law in support of his rejection for lack of written description.

Claims 28-32 and 38-39 are rejected under Section 112, first paragraph, as failing to comply with the written description requirement. The examiner urges that appellants are claiming a subgenus of humanized antibodies, but disclose only a single monoclonal antibody, LL2. The examiner has cited *In re Gosteli*, 872 F.2d at 1008 (Fed.Cir. 1989) as holding that disclosure of two chemical compounds within a subgenus did not describe that subgenus. *Gosteli* was an attempt to claim the right of foreign priority for a subgenus claim reciting a total of 21 specific compounds. The foreign priority document disclosed only two compounds within the subgenus. The CAFC found that the two compounds were an inadequate written description of the subgenus of 21 compounds.

The examiner also has cited *Enzo Biochem, Inc. v. Gen-Probe, Inc.* 323 F.3d 956 (Fed.Cir. 2002), commonly referred to as "*Enzo II.*" *Enzo* involved a US patent claiming nucleic acid probes that preferentially hybridize to the DNA of *Neisseria gonorrhoeae*, which causes gonorrhea, over the DNA of *N. meningitidis*, which causes meningitis. In *Enzo I*, 285 F.3d 1013 (Fed.Cir. 2002), the CAFC had held that an inventor must obtain a new compound and resolve its structure before he or she is entitled to patent it. The Federal Circuit reversed itself on rehearing (*Enzo II*). In the opinion, the Federal Circuit referred back to *Regents of the University of California v. Eli Lilly & Co.*, (119 F.3d 1559 (Fed.Cir. 1997), where it had considered claims to genetic material that had only been defined by function, and found that the functional description alone was insufficient to satisfy the written description requirement. However, the Federal Circuit clearly stated that not all functional descriptions of genetic material would fail to meet the written description requirement, particularly not when functional characteristics are coupled with a known or disclosed correlation between function and structure.

The examiner also has cited *Noelle v. Lederman*, 355 F.3d 1343 (Fed.Cir. 2004). Claim 1 of Lederman's patent was directed to "a monoclonal antibody, which specifically binds and forms a complex with the 5c8 antigen located on the surface of activated T cells and thereby inhibits T cell activation of B cells, the 5c8 antigen being an antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds." The court stated that:

> The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath,* 935 F.2d at 1563-64 (emphasis in original). Thus, the test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. An earlier application that describes later-claimed genetic material only by a statement of function or result may be insufficient to meet the written description requirement. *See Regents,* 119 F.3d at 1566. This court has held that a description of DNA "`requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Id.* (quoting *Fiers v. Revel,* 984 F.2d 1164, 1170 (Fed. Cir.1993)). Therefore, this court has held that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1566-67 (quoting *Fiers,* 984 F.2d at 1171).

A further case cited by the examiner is *In re Curtis*, 354 F3d 1347 (Fed.Cir. 2004), in which the examiner has highlighted the statement that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when, as is the case here, the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." The claim in *Curtis* was directed to an improved dental floss made of expanded polytetrafluoroethylene ("PTFE") filaments coated with a friction enhancing coating. The friction enhancing coating language was not found in the original priority document, which disclosed only a microcrystalline wax (MCW) coating, but first appeared in a CIP. The court found the original disclosure of MCW did not support a genus of friction enhancing coatings.

Finally, the examiner cites *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed.Cir., 2004). The claimed invention in *Rochester* was directed to a method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment. The examiner cites the court's statement that "Rochester also attempts to distinguish *Fiers, Lilly,* and *Enzo* by suggesting that the holdings in those cases were limited to composition of matter

claims, whereas the '850 patent is directed to a method. We agree with the district court that that is 'a semantic distinction without a difference.'"

The present facts differ from those in the case law cited by the examiner.

The clear focus of the examiner's arguments in this case all center on the notion that the written description requirement for a claimed genus must be satisfied through sufficient description of a representative number of species, and that appellants have described only one member of the genus, hLL2. However, appellants here are not claiming a "genus" of humanized antibodies, of which hLL2 would be a species. ***Appellants are claiming a method,*** the implementation of which can be used to produce humanized antibodies. The inclusion within the four corners of the specification of other species (antibodies other than humanized LL2) produced according to the method would not further describe the method, and was unnecessary to apprise those of ordinary skill in the art that appellants were in possession of a method of designing humanized antibodies.

Each of the cases above that have been cited by the examiner relate to patents or applications in which the claimed invention was directed to a product. The examiner cites *Rochester* as being an example of a written description case where the claims were method claims. However, the claims at issue in *Rochester* were not directed to the screening methods used to obtain the PGHS-2 compounds, rather they were directed to a method of *using* any compound that selectively inhibits PGHS-2 activity. Thus, they were an attempt to claim treatment methods using any compound meeting a functional definition where "the inventors had neither possession nor knowledge of such a compound." The court was not fooled, and characterized the claim format as a matter of semantics.

In clear contrast, the present claims are directed to a method of designing humanized antibodies. The claims are not directed to a genus of humanized antibodies or to a method of using a genus of humanized antibodies. Thus, all of the cited case law easily can be distinguished on this basis. Written description only requires a description ***of that which is claimed*** (see quote from *Noelle* above). The claimed invention is a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody which is described in the specification. It is exemplified by a disclosure of application of the method to humanization of the LL2 antibody. One

way of showing possession of an invention is by an actual reduction practice,[1] and the humanization of LL2 in the present disclosure is just such an actual reduction to practice of the presently claimed method.

The proper issue in this case is whether appellants apprised those reading the disclosure that they were in possession of a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody by (i) comparing the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of two or more human antibodies, (ii) selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody; and (iii) incorporating the selected framework regions with the corresponding light and heavy chain complementarity determining regions of a monoclonal antibody to be humanized, thereby to design humanized light and heavy chain variable domain amino acid sequences. The original disclosure fulfills that requirement. All of the steps are laid out in detail, and exemplified by frequent reference to the humanization of the LL2 antibody.

One skilled in the art immediately would recognize that appellants were in possession of a method applicable to the humanization of antibodies *generally*. The specification notes that "an important aspect of this invention is that antibody variable domains can be modeled by computer modeling" and that "once the sequences for the hLL2 VK and VH domains are designed, CDR engrafting can be accomplished by gene synthesis using long synthetic DNA oligonucleotides as templates and short oligonucleotides as primers in a PCR reaction." The clearly outlined steps of the method were unquestionably in appellants' possession.

Thus, the present method claims are readily distinguishable on the facts from the cited cases. As noted in *Enzo II*, citing *Vas-Cath*, "the invention is, for purposes of the "written description" inquiry, *whatever is now claimed*." Therefore, the proper inquiry is "whether a person of ordinary skill in the art would recognize that the appellant possessed what is claimed in the later filed application as of the filing date of the earlier filed application" (*Enzo II, supra*). The original specification, as filed on August 12, 1994, clearly informs a person of ordinary skill in the art that

[1] See, e.g., MPEP 2163, Section I, second sentence in third full paragraph: "Possession may be shown in a variety of ways including description of an actual reduction to practice."

appellants possessed a method for humanizing antibodies in which each variable (V) region framework (FR) sequence of a non-human antibody is compared to a corresponding variable (V) region framework (FR) sequence of a human antibody to determine the degree of sequence homology between the non-human antibody FRs and the human antibody FRs, and then each FR in the non-human antibody is replaced with a human antibody FR which exhibits sequence homology to the non-human antibody FRs. Thus, the specification discloses:

> By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat database (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference, the human REI (FIG. 1A, SEQ ID NO. 6) and EU (FIG. 1B, SEQ ID NOS. 9 and 8) sequences were found to exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain. Based on the results of computer modeling studies (FIGS. 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (FIG. 1).

It is clear that each variable region framework sequence was compared to its corresponding framework region in a database of human antibodies, and that replacement of framework regions was based on sequence homology. This is the invention claimed in the present application and the specification shows that appellants possessed this invention as of their earliest filing date.

In short, appellants are not presently claiming a genus of humanized antibodies, but rather a method for designing humanized antibodies. Thus, arguments by the examiner that "a patentee will not be deemed to have invented species sufficient to constitute a genus by virtue of having disclosed a single species when…the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed" are not on point. The issue must always be approached from the perspective of what it *claimed*. What is claimed is a general method of designing amino acid sequences for humanized antibodies. The written description leaves no doubt that this method was in appellants' possession as of their earliest filing date.

One further point that has been raised by the examiner requires discussion in the context of the present rejection. The examiner urged in the Advisory Action that:

> the specification does not fully develop the concept that there are universal or best fit human frameworks for humanization in which just any non-human CDRs may be grafted and retain the antigen specificity and affinity of the parental non-human antibody. Further, in light of the prior art, *e.g.*, Groman *et al.*, such a universal property appears to be unpredictable since different antibodies will have different amino acids in the framework which are important for antigen binding and stability.

It should be noted, in this regard, that appellants have not argued that there are universal or best fit frameworks which work with any CDRs. Moreover, the fact that application of the method requires the exercise of some experimentation in terms of comparing the framework regions of various human antibodies to the framework regions of the non-human antibody which is to be humanized, and selecting those which provide the "best fit" for *particular* CDRs in terms of homology does not show that appellants did not possess the invention. Nor does the fact that application of the method does not lead to selection of the same framework regions for every antibody humanized lead to such a conclusion. These are both red herrings. The question, quite simply, is whether one of ordinary skill in the art would come away from reading appellants' disclosure with an understanding that appellants possessed a method of designing amino acid sequences for humanized antibodies. The clear answer is that the skilled artisan would conclude that appellants did indeed possess the steps of the method as set forth in claim 28, even prior to its amendment after final rejection. As amended after final, claim 28 more particularly directs the skilled artisan to those framework regions that have worked repeatedly in the design of humanized amino acid sequences for antibodies, thereby further minimizing the scope of experimentation to be undertaken when practicing the present method. A written description of the selection of this combination of framework regions is unambiguously set for the specification.

By following the written description provided in the specification, other humanized antibodies have been produced by means of the claimed method.

Appellants' invention provides a method of producing humanized antibodies, and appellants have used this invention to produce other humanized antibodies, as summarized in the following table.

Antibody	Variable domain	FR1	FR2	FR3	FR4	Disclosed in
hLL2	VH	EU	EU	EU	NEWM	Present application
	Vk	REI	REI	REI	REI	US 5,789,554
hA19	VH	EU	EU	EU	NEWM	US 7,109,304
	Vk	REI	REI	REI	REI	
hA20	VH	EU	EU	EU	NEWM	US 7,151,164
	Vk	REI	REI	REI	REI	
hMN3	VH	EU	EU	EU	KOL	WO04029093
	Vk	REI	REI	REI	REI	
Immu31	VH	EU	EU	EU	NEWM	Qu *et al.*, *Clin Cancer Res.* Oct;5(10Suppl):3095s-3100s (1999)
	Vk	REI	REI	REI	REI	
hRS7	VH	RF-TS3	RF-TS3	RF-TS3	NEWM	WO03074566
	Vk	SA-IA'CL	SA-IA'CL	SA-IA'CL	SA-IA'CL	
hMN14	VH	KOL	KOL	KOL	KOL	US 20040191248
	Vk	REI	REI	REI	REI	
h1F5	VH	EU	EU	EU	NEWM	US 20030219433
	Vk	REI	REI	REI	REI	
hMu9	VH	EU	EU	EU	NEWM	US 20050169926
	Vk	WOL	WOL	WOL	WOL	
hL243	VH	RF-TS3	RF-TS3	RF-TS3	NEWM	US 20060210475
	Vk	REI	REI	REI	REI	
hLL1	VH	RF-TS3	RF-TS3	RF-TS3	NEWM	US 20040115193
	Vk	HF-21/28	HF-21/28	HF-21/28	HF-21/28	

Applications subsequently filed by Leung, US20030040606A1 and US20050033028A1 (Examiner: David Blanchard) also disclose production of humanized antibodies by the presently claimed method, as do articles by Leung *et al.* (Leung *et al.*, *Hybridoma* v13:469-475 (1994) and Leung *et al.*, *Molecular Immunology*, v32:1413-1427 (1995)). Thus, the method has been a useful tool for producing humanized antibodies generally.

Solely in an attempt to advance prosecution in this case, appellants amended the only independent claim after final rejection to recite a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody in which the heavy chain FR4 is selected from the human NEWM antibody, the light chain framework regions are selected from the human REI antibody, and the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody. Referring to the chart above, it can be seen that this particular strategy has been especially useful, and is found in the constructs used in five of the antibodies listed in the table. Appellants' specification particularly directs a skilled artisan to this combination of framework regions, and thus also evidences possession of claim 28 as amended following final rejection.

The examiner has countered appellants' showing of other antibodies designed by appellants using their method with the comment that "the issue is not whether one of skill in the art could make and use the claimed method, which goes more towards enablement, but rather whether the written description necessarily discloses the claimed subject matter."[2] Appellants did not provide the listing of other antibodies in order to provide other members of a genus. As noted above, *appellants are not claiming a genus*. The listing of antibodies was provided in response to a comment by the examiner that "there is no evidence in the disclosure *or anywhere else in the record* showing applicant conveyed that any other CDRs other than LL2 are suitable for grafting onto the human REI light chain frameworks and unto the human EU and NEWM heavy chain frameworks."[3] Thus, appellant thought perhaps the examiner was concerned with whether the present method could be practiced to produce other antibodies with these particular human frameworks. The listing was provided merely to confirm the broad applicability and success of the presently claimed method in the humanization of antibodies.

[2] Advisory Action at page 2, lines 41-42.
[3] Office Action dated February 20, 2007, at page 8, lines 14-17.

B. The rejection of claims 28, 29, 31 and 32 under 35 USC 102(b) based on Leung *et al.* (US 5,789,554).

The instant application is a continuation of USSN 09/741,843, filed 12/22/00, which was a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which was a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which was a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/289,576, filed 8/12/94, as detailed above under Section A of this Brief on Appeal.

C. The rejection of claims 28, 29, 31 and 32 under 35 USC 102(b) based on Leung *et al.* (*Molecular Immunology*, 32(17018):1413-1427 (1995).

The instant application is a continuation of USSN 09/741,843, filed 12/22/00, which was a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which was a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which was a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/289,576, filed 8/12/94, as detailed above under Section A of this Brief on Appeal.

VIII. CONCLUSION

For these reasons, the Board is requested to reverse the decision of the examiner and pass the present case to issuance.

Respectfully submitted,

ROSSI, KIMMS & McDOWELL LLP

MARCH 31, 2008

DATE

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CLAIMS APPENDIX

1-27. (Canceled)

28. (Previously presented) A method of designing amino acid sequences of variable domains of a humanized monoclonal antibody comprising:

(a) comparing the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of two or more human antibodies;

(b) selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody; and

(c) incorporating the framework regions selected in step (b) with the corresponding light and heavy chain complementarity determining regions of the monoclonal antibody to be humanized, to design humanized light and heavy chain variable domain amino acid sequences

wherein the heavy chain FR4 is selected from the human NEWM antibody, the light chain framework regions are selected from the human REI antibody, and the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody.

29. (Previously presented) The method according to claim 28, further comprising retaining selected amino acid residues from the framework regions of the monoclonal antibody to be humanized in the corresponding framework regions of the humanized variable domains where said selected amino acids are predicted to have contacts with said complementarity determining regions.

30. Canceled.

31. (Previously presented) The method according to claim 29, wherein said selected amino acid residues are within a 4.5 Angstrom radius of any atoms within a complementarity determining regions of the light or heavy chain of the humanized monoclonal antibody.

32. (Previously presented) The method of claim 28, further comprising:

(d) preparing a DNA sequences encoding the humanized light and heavy chain variable domain amino acid sequences;

(e) operably incorporating the variable domain DNA sequences into at least one vector comprising DNA sequences encoding the constant domains of the human light and heavy chain regions;

(f) introducing the at least one vector into a cell; and

(g) culturing the cell containing the at least one vector under conditions to produce the humanized monoclonal antibody.

33-43. (Canceled)

EVIDENCE APPENDIX

No evidence was submitted during prosecution.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.